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SPECIAL ARTICLE

Hereditary gastrointestinal cancers: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

N. Stjepanovic[1], L. Moreira[2], F. Carneiro[3,4,5,6], F. Balaguer[2], A. Cervantes[7], J. Balmaña[1] & E. Martinelli[8], on behalf of the ESMO Guidelines Committee*

[1]Medical Oncology Department, University Hospital Vall d'Hebron, Barcelona; [2]Gastroenterology Department, Hospital Clínic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Barcelona, Spain; [3]Institute of Molecular Pathology and Immunology of the University of Porto (IPATIMUP), Porto; [4]Instituto de Investigação e Inovação em Saúde (i3S), Porto; [5]Medical Faculty of the University of Porto, Porto; [6]Centro Hospitalar Universitário São João, Porto, Portugal; [7]CIBERONC, Department of Medical Oncology, Biomedical Research Institute INCLIVA, University of Valencia, Valencia, Spain; [8]Dipartimento di Medicina di Precisione, Università degli Studi della Campania Luigi Vanvitelli, Napoli, Italy

**Correspondence to:* ESMO Guidelines Committee, ESMO Head Office, Via Ginevra 4, 6900 Lugano, Switzerland. E-mail: clinicalguidelines@esmo.org

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Knowledge of genetic susceptibility to gastrointestinal cancers is constantly evolving with identification of new genes. Similarly, a better understanding of the genotype/phenotype relationship in patients with Lynch syndrome (LS) or familial adenomatous polyposis (FAP) is leading to more individualised surveillance recommendations. In addition, molecular profiling of patients with cancer has been shown to guide targeted therapies, such as immunotherapy. Specialists involved in the care of patients with gastrointestinal cancer should be familiar with the main hereditary cancer syndromes and refer patients to specialised cancer genetic units for adequate genetic counselling and to address specific concerns associated to each genetic susceptibility. These guidelines aim to summarise the evidence-based data on hereditary colorectal cancer (CRC), gastric cancer (GC) and pancreatic cancer (PC) and provide useful clinical recommendations for identification and management of patients with hereditary gastrointestinal cancers.

Hereditary non-polyposis colorectal cancer syndrome (Lynch syndrome)

Prevalence and penetrance

LS accounts for 1%–3% of all CRC diagnoses [1]. It is caused by germline mutations in one of the mismatch repair (*MMR*) genes (*MLH1*, *MSH2*, *MSH6* or *PMS2)* or epithelial cell adhesion molecule (*EPCAM*, which causes epigenetic silencing of *MSH2)* and has an autosomal dominant inheritance. More than 70% of mutations are identified in *MLH1, MSH2 or EPCAM* in tumours with microsatellite instability (MSI)-high.

LS is characterised by an increased lifetime risk of CRC (30%–73%) and extracolonic malignancies such as endometrial (30%–51%), ovarian (4%–15%), gastric (up to 18%), small bowel (3%–5%), urinary tract (2%–20%), pancreatic (4%), brain or cutaneous gland tumours [2–4]. The carriers of pathogenic variants in *MLH1* and *MSH2* genes have a substantially higher risk of CRC cancer with younger age at diagnosis compared with carriers of *MSH6* or *PMS2* pathogenic variants. The cumulative incidence of endometrial and urinary tract cancers is higher in *MSH2* carriers [5]. Data on cancer risk estimates for carriers of an *EPCAM* deletion is still limited.

Historically, two LS clinical phenotypes have been described in those individuals with germline *MMR* gene pathogenic variants presenting with the combination of central nervous system tumours (Turcot syndrome) or combination of cutaneous gland tumours (Muir–Torre syndrome) [6, 7]. Recently, a third phenotype denominated constitutional or biallelic *MMR* deficiency (CMMRD) has been described in those individuals who are homozygous or compound heterozygotes for pathogenic variants in the *MMR* gene and is characterised by café-au-lait spots and childhood-onset tumours [8, 9].

Clinical and molecular diagnosis

Alterations in the *MMR* genes lead to accumulation of errors during DNA replication, especially in repetitive sequences known as

microsatellites, causing MSI in the LS-related tumours. Due to the alterations in the *MMR* genes, the LS tumours may lack the expression of the corresponding MMR protein [tested by immunohistochemistry (IHC) staining]. MMR IHC testing on CRC tumours has a sensitivity and specificity of 94% and 88%, respectively, and is highly correlated to MSI status [10].

Approximately 10% of CRCs display loss of expression of MLH1 and MSI due to somatic hypermethylation of the *MLH1* promoter, often associated with *BRAF V600E* mutation in sporadic CRC. Therefore, if loss of MLH1 expression (alone or concurrently with loss of PMS2 expression) is observed, methylation analysis of the *MLH1* promoter in the tumour and/or analysis for somatic *BRAF V600E* mutation should be carried out first [III, B]. Similarly, if loss of MLH1 expression (alone or concurrently with loss of PMS2 expression) is observed in GCs, hypermethylation of the MLH1 promoter should be ruled out first [III, B]. Double somatic mutations in CRC and endometrial cancer (EC) have recently been recognised by tumour sequencing. Tumours with double somatic mutations in *MMR* genes have a molecular phenotype that mimic LS cancers, as they present with MSI and lack the expression of MMR proteins [11]. Therefore, somatic *MMR* gene testing for patients with unexplained abnormal tumour screening is suggested [III, B] [11].

Clinical criteria used for identification of individuals at risk of LS, such as Amsterdam II criteria and revised Bethesda guidelines are based on age and family history of cancer (Table 1) [12, 13]. Due to the limited sensitivity and specificity of the clinical criteria, a broader CRC molecular screening with MMR IHC and/or MSI via polymerase chain reaction was proposed (Figure 1). The universal MMR IHC tumour testing in CRC patients has been shown to be more sensitive than the Bethesda guidelines for the identification of individuals at risk of LS (100% versus 87.8%) [14]. In addition, clinical criteria are gradually being surpassed by the evolving universal MMR IHC due to the role of MSI as a biomarker for predicting good response to treatment with immune checkpoint inhibitors in advanced cancer patients [15, 16]. Germline genetic testing can be considered in patients who fulfil the Amsterdam criteria, regardless of the *MMR* status. If multigene panel testing is available, *MUTYH, POLE* and *POLD1* genes can be added to *MMR* genes, especially in those diagnosed at <50 years [III, C] [17, 18].

Similarly, MMR IHC and/or MSI screening followed by analysis of *MLH1* promoter hypermethylation (if loss of expression of MLH1) is also recommended for women with EC, since 2%–3% of ECs are associated with LS [III, B] [19].

For those individuals where no tumour tissue is available for molecular testing, prediction models that estimate the likelihood of finding an *MMR* gene pathogenic variant (i.e. PREMM model) constitute an effective clinical tool to consider referral for genetic testing [III, B] [20].

Pathogenic genetic alterations might be frameshift, nonsense or splice site mutations that lead to truncating or unstable proteins, but large deletions and rearrangements are also common. Therefore, full germline genetic testing should include both DNA sequencing and large rearrangement analysis [III, A].

Surveillance and risk reduction

For individuals with LS, prevention and early detection of associated cancers by active surveillance can increase survival and improve quality of life. Thanks to advances in the genotype/phenotype correlation for LS patients, the surveillance protocol may be tailored according to the genetic alteration and family history of cancer (Table 2).

Colorectal surveillance. Accelerated adenoma-carcinoma sequence has been demonstrated in individuals with LS. Periodic colonoscopy surveillance allows the resection of polyps and identification of early-stage CRC. Colonoscopies carried out every 3 years have shown a CRC incidence and mortality reduction of 62% and 66%, respectively, while more frequent screening has been associated with earlier stage of CRC at diagnosis and up to 72% decrease in CRC mortality [21–23]. Since the diagnosis of CRC before age 25 is unlikely in individuals with LS, and the CRC risk in *MSH6* and *PMS2* mutation carriers is substantially lower than for *MLH1* and *MSH2* ones, onset of colonoscopy surveillance is recommended at the age of 25 years for *MLH1* and *MSH2* mutation carriers and at the age of 35 years for *MSH6* and *PMS2* mutation carriers [III, C] [24, 25]. In all cases, age of onset in the youngest member of the family is to be considered and surveillance should be started 5 years earlier [V, B]. Surveillance colonoscopy every 1–2 years in asymptomatic individuals with LS is recommended [III, A] [5].

Chromoendoscopy with indigo carmine added to the standard colonoscopy has been shown to be substantially more effective than colonoscopy alone in LS individuals [26]. High-quality colonoscopy carried out in dedicated centres is advised [IV, C].

Gastric and small bowel surveillance. There is no clear evidence to support upper gastrointestinal endoscopy surveillance in all LS patients. Consider testing and treating *Helicobacter pylori* (*H. pylori*) in all mutation carriers [27]. In regions with high GC incidence and in families with a history of gastric neoplasms, surveillance with upper endoscopy may be considered every 1–3 years, starting at the age of 30–35 years [27]. Routine surveillance of the small bowel in LS has a high rate of false-positive findings and it is not considered to be cost-efficient [IV, C].

Pancreatic surveillance. Annual magnetic resonance imaging (MRI) and/or endoscopic ultrasound (EUS) surveillance in individuals with LS and one first-degree relative (FDR) affected with PC may be considered, although more supporting evidence is needed [IV, C] [28].

Gynaecological surveillance. Transvaginal ultrasound (TV US) has shown poor sensitivity and specificity for the diagnosis of EC in women with LS, while endometrial sampling could identify patients with premalignant endometrial lesions or asymptomatic endometrial carcinomas. Prophylactic hysterectomy and/or bilateral salpingo-oophorectomy reduce the incidence of EC and ovarian cancer in the LS population, although the survival benefit has not been demonstrated [29].

We recommend an annual gynaecological examination, TV US with cancer antigen 125 (CA 125) analysis and endometrial biopsy from age 30 to 35 years [IV, C]. Prophylactic hysterectomy with bilateral oophorectomy is an option that might be discussed and considered for mutation carriers who have completed childbearing or are postmenopausal [IV, C].

Table 1. Amsterdam criteria II [12] and revised Bethesda [13] guidelines

Amsterdam criteria II

At least three relatives must have a cancer associated with LS (colorectal, cancer of the endometrium, small bowel, ureter or renal pelvis); all of the following criteria should be present:

- One must be a FDR of the other two
- At least two successive generations must be affected
- At least one relative with a cancer associated with LS should be diagnosed before age 50
- FAP should be excluded in the CRC case(s) (if any)
- Tumours should be verified whenever possible

Revised Bethesda guidelines

Tumours from individuals should be tested for MSI in the following situations:

- CRC diagnosed in a patient who is younger than 50 years of age
- Presence of synchronous or metachronous colorectal or other LS-related tumours[a], regardless of age
- CRC with MSI-high histology[b] diagnosed in a patient who is younger than 60 years of age
- CRC diagnosed in a patient with one or more FDRs with an LS-related cancer, with one of the cancers being diagnosed below age 50
- CRC diagnosed in a patient with two or more first- or second-degree relatives with LS-related cancer regardless of age

[a]LS-related cancers include colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain (usually glioblastoma), small intestinal cancers, as well as sebaceous gland adenomas and keratoacanthomas.
[b]Presence of tumour infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet ring differentiation or medullary growth pattern.
CRC, colorectal cancer; FAP, familial adenomatous polyposis; FDR, first-degree relative; LS, Lynch syndrome; MSI, microsatellite instability.
Adapted from Vasen et al. [12] and Umar et al. [13] with permission.

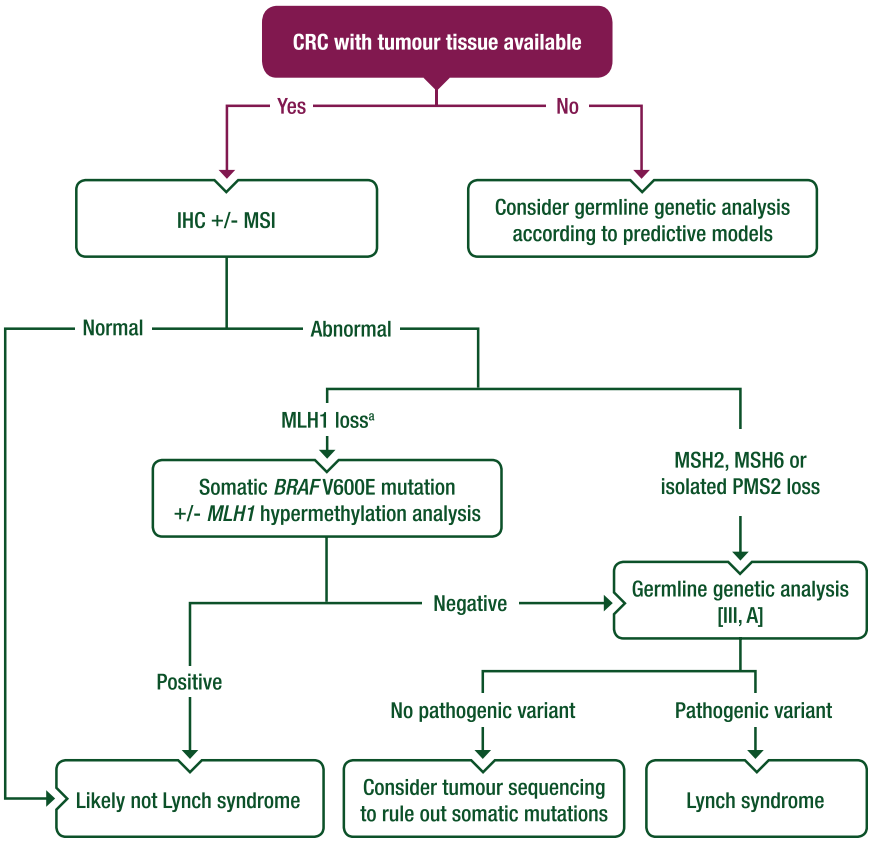

Figure 1. Algorithm for molecular diagnosis of Lynch syndrome.
[a]If the loss of expression of MLH1 is concurrent with the loss of expression of MSH2 or MSH6 a germline genetic analysis should be recommended.
CRC, colorectal cancer; IHC, immunohistochemistry; MSI, microsatellite instability.

Table 2. LS surveillance recommendations

Site	Technique	Age (years)	Interval (years)
Colorectum	Colonoscopy	• *MLH1/MSH2*: 25[a,b] • *MSH6/PMS2*: 35	1–2
Uterus	TV US Endometrial biopsy	30–35	1
Ovaries	CA 125 + TV US	30–35	1
Stomach	UGI endoscopy[c] Consider testing *Helicobacter pylori*	30–35	1–3
Other LS-associated cancers	None[d]		

[a]Or 5 years before the earliest CRC, if diagnosis <25 years.
[b]Consider later age for *MSH6* carriers.
[c]Consider in high-incidence countries or family history of gastric cancer.
[d]Consider pancreatic/urinary tract cancer surveillance if family history.
CA 125, cancer antigen 125; CRC, colorectal cancer; LS, Lynch syndrome; TV, transvaginal; UGI, upper gastrointestinal; US, ultrasound.

Urinary tract surveillance. Urine cytology surveillance in individuals with LS has a poor sensitivity (29%) and a high rate of false-positive results, while the benefit of the US screening is unknown [30]. We only recommend urinary tract surveillance under a research protocol [IV, C].

Chemoprevention. The Colorectal Adenoma/Carcinoma Prevention Programme 2 (CAPP2) has shown a 60% reduction in the incidence of CRC- and other LS-associated tumours among those individuals treated with 600 mg daily aspirin taken for at least 2 years versus placebo [31]. Aspirin may be considered as a cancer prevention measure in individuals with LS, although the optimal dose has still not been determined and is the objective of the ongoing CAPP3 study that compares daily aspirin at 600, 300 and 100 mg [I, C].

Environmental and lifestyle factors. Smoking and obesity increase the risk of adenomas and CRC in LS [32]. Patients are advised to refrain from smoking and stay within normal weight range [III, C].

Cancer treatment

Colorectal surgery. It has been shown that there was an increased risk of metachronous CRC after partial colectomy and that the quality of life was similar after partial and total colectomy with ileorectal anastomosis (IRA) [19]. Therefore, an extended colectomy may be an option in patients with LS undergoing primary surgery for CRC, especially in younger patients [IV, C].

Systemic treatment. Presence of MSI is a demonstrated prognostic factor and remains controversial as predictive for current chemotherapy (ChT) regimens in CRC and GC. Current evidence does not allow definitive recommendations regarding ChT regimens based on the MMR or MSI status [33]. The MMR- or MSI-deficient status may be useful to determine the subset of stage II CRC patients who present a low risk of recurrence and in whom an adjuvant ChT may not be necessary [II, C] [34].

Several studies have demonstrated that MMR-deficient tumours harbour a high mutational load, and express numerous neoantigens that makes them sensitive to immunotherapy. Two immune checkpoint inhibitors have demonstrated substantial responses in patients with advanced MMR-deficient cancers and have received accelerated approval by the United States Food and Drug Administration (FDA): pembrolizumab for any MMR-deficient solid tumour and nivolumab for colorectal MMR-deficient tumours [15, 16].

Familial colorectal cancer X syndrome

This syndrome represents up to 40% of families who fulfil the Amsterdam criteria for hereditary non-polyposis colon cancer but do not harbour a tumour MMR deficiency or an underlying germline *MMR* gene alteration [35]. Risk of cancer in these families seems to be limited to the colorectum, and colonoscopy surveillance at 3–5-year intervals, starting at age 40 or 10 years earlier than the age at diagnosis of the youngest case in the family may be considered [IV, C].

Constitutional mismatch repair-deficiency syndrome

Patients with biallelic mutations in one of the *MMR* genes are usually affected with childhood cancers. There is a high-incidence of CRC, adenomatous polyposis and small bowel tumours, haematological tumours (leukaemia or lymphoma), brain, endometrium and urinary tract tumours. Two expert consensuses have proposed a surveillance approach that includes semestral blood work and abdominal US, annual brain MRI, upper endoscopy and colonoscopy and consideration of annual whole-body MRI. Both consensuses acknowledge the lack of robust evidence and the need for more research [36, 37].

Lynch-like syndrome

This refers to patients who resemble LS due to the presence of MMR deficiency or MSI (excluding *MLH1* hypermethylation) but lack a germline mutation. In these cases, *MMR* genetic testing on tumour DNA would recognise that 50%–70% of these cases harbour biallelic somatic mutations that might explain the abnormal IHC and/or MSI results [38]. Therefore, ruling out a sporadic somatic biallelic inactivation of these genes would spare an intensive surveillance of Lynch-associated tumours in relatives considered potentially at risk.

Hereditary polyposis colorectal cancer syndromes

Colorectal polyposis is a group of syndromes characterised by multiple polyps in the large intestine and an increased risk of CRC, as well as extraintestinal manifestations. Depending on the histology of the polyps, they are classified into adenomatous, serrated polyposis and hamartomatous polyposis.

Familial adenomatous polyposis

Prevalence and penetrance. FAP is an autosomal dominant inherited disorder associated with germline mutations in the adenomatous polyposis coli (*APC)* gene and characterised by the presence of multiple colorectal adenomas. In its classical form, FAP patients have a near 100% risk of developing CRC at an early age if prophylactic colectomy is not carried out. It represents <1% of all cases of CRC and constitutes the most frequent cause of polyposis with a known genetic cause [39].

Clinical and molecular diagnosis. Clinical diagnosis is based on two main phenotypes, the classical form characterised by >100 adenomas along the entire colon, and the attenuated phenotype that presents between 10 and 100 adenomas, preferentially localised in the right colon and with a later onset. It is associated with a broad spectrum of extracolonic tumours, including hepatoblastoma in children, duodenal, pancreatic, thyroid and brain cancers. Germline mutation in the *APC* gene is found in 80% of the classical FAP and only in 10% of attenuated cases [40]. Mutations located between codons 1250 and 1464 of the *APC* gene have been associated with more severe forms of FAP. In 30%–40% of cases, no family history of FAP is present, thus suggesting a *de novo* origin [41].

Full germline genetic testing should include both DNA sequencing and large rearrangement analysis; *APC* analysis should include large rearrangements [III, A]. With the incorporation of multigene panels, the genetic testing can be carried out as a single analysis of multiple genes involved in colorectal adenomatous polyposis (*APC, MUTYH, POLE, POLD1, NTHL1*) [42, 43].

Surveillance and risk reduction. Surveillance should be done in all mutation carriers as well as in all members of any given family for whom the causative germline mutation cannot be identified (Tables 3 and 4).

Colorectal surveillance: In patients with classical FAP, flexible sigmoidoscopy or colonoscopy should be carried out every 2 years, starting at age 12–15 years [44]. Once adenomas are detected, colonoscopy should be carried out every 1–2 years until colectomy is planned. In patients with *APC*-attenuated FAP (AFAP), colonoscopic surveillance should be done every 1–2 years, starting at the age of 18–20 years [III, C] [44].

Treatment of classical FAP is surgical and should be carried out before the age of 25 years. The choice of surgical technique [total colectomy with IRA or proctocolectomy with ileal pouch-anal anastomosis (IPAA)] depends on the age at diagnosis, severity of the polyposis, presence of rectal polyps and risk of developing desmoids [45]. Annual or biannual endoscopic follow-up is recommended after surgery in patients with FAP [III, B].

Secondary chemoprevention with the use of non-steroidal anti-inflammatory drugs (NSAIDs) has been shown to reduce the number and extent of colorectal adenomas and, less reliably, duodenal adenomas. Due to the cardiovascular risk of NSAIDs (particularly for cyclooxygenase-2 [COX-2] inhibitors), no single chemoprevention drug has an approved indication for the management of FAP or MUTYH-associated polyposis (MAP). Their use needs to be balanced with the side-effects [II, B] [46].

Table 3. Classical FAP surveillance guidelines

Site	Technique	Age (years)	Interval (years)
Colorectal	Sigmoidoscopy and colonoscopy (if adenomas)[a]	12–15	1–2
Duodenum	Gastroduodenal endoscopy (front and side view)	25–30	1–5[b]
Thyroid	Cervical US or cervical palpation	25–30	1
Liver	Abdominal US Serum alpha foetoprotein	0.5[c]	1
Desmoids	CT/MRI[d]		

[a]If adenomas are found at sigmoidoscopy, carry out annual colonoscopies until colectomy.
[b]Periodicity according to the Spigelman stage.
[c]Until age 7 years.
[d]If family history or symptoms. Periodicity is not well-established.
CT, computed tomography; FAP, familial adenomatous polyposis; MRI, magnetic resonance imaging; US, ultrasound.

Gastric and small bowel surveillance: Fundic gland polyps are frequently found in FAP patients, while gastric neoplasias are uncommon. Duodenal polyps are present in up to 90% of FAP patients, and duodenal cancer is the second cause of cancer death in FAP, with a cumulative lifetime risk of 5% [47]. Therefore, gastroduodenal endoscopy surveillance is recommended every 5 years starting at 25–30 years of age or at the time of diagnosis of colonic polyposis for both classical FAP and AFAP patients [III, C]. If adenomas are detected, surveillance is guided by the Spigelman classification based on the number, size and histology of adenomas (Table 5) [47]. For Spigelman stage I, the upper endoscopy is recommended every 5 years and for Spigelman stage II every 3 years, while for more advanced stages the intervals should be shortened to every 1–2 years for Spigelman stage III and every 6 months or prophylactic surgery for Spigelman stage IV [III, B] [44]. Additional side-viewing endoscopic surveillance is recommended for patients with Spigelman stages III and IV and/or papillary involvement. Duodenal adenomas are usually managed by endoscopic polypectomy, although surgery (duodenectomy or duodenal-pancreatectomy) may be necessary in advanced cases. The risk of cancer in jejunum and ileum is extremely low; therefore, routine surveillance with endoscopic capsule is not recommended [V, C].

Extraintestinal surveillance: Some experts recommend annual thyroid palpation and/or ultrasonography, due to a 2% lifetime risk of thyroid cancer in FAP patients [44]. Surveillance for hepatoblastoma has been suggested with biannual determination of serum alpha foetoprotein levels and abdominal ultrasonography in children of patients with FAP, from birth to 7 years of age [IV, C] [48].

Development of desmoid tumours is mainly related to a positive family history, abdominal surgery and site of the mutation and can occur inside the abdomen or in the abdominal wall. In this setting, regular physical examination and abdominal computed tomography or MRI should be carried out. The options for treatment include pharmacological treatment (NSAIDs

Table 4. Other polyposis syndromes surveillance guidelines

Syndrome	Site	Technique	Age (years)	Interval (years)
Attenuated FAP	Colorectal	Colonoscopy	18–20	1–2
	Duodenum	Gastroduodenal endoscopy (front and side view)	25–30	1–5[a]
MAP	Colorectal	Colonoscopy	18–20	1–2
	Duodenum	Gastroduodenal endoscopy (front and side view)	25–30	1–5[a]
PPAP	Colorectal	Colonoscopy	18–20	1–2
	Uterus	TV US	30–35	1
SP	Colorectal	Colonoscopy	45	1–2[b]
PJ	Colorectal	Colonoscopy	8[c]	1–3
	Gastric	Gastroduodenal endoscopy	8[c]	1–3
	Small bowel	Capsule endoscopy or MRI enterography	8[c]	1–3
	Pancreas	Endoscopic ultrasonography or MRI	30	1
Juvenile polyposis	Colorectal	Colonoscopy	15	1–3
	Gastric	Gastroduodenal endoscopy	15	1–3

[a]Periodicity according to the Spigelman stage.
[b]FDR: starting at 45 or 10 years earlier than the affected relative. If no polyps, repeat every 5 years.
[c]Basal colonoscopy at age 8. If negative for polyps, re-start surveillance at age 18.
FAP, familial adenomatous polyposis; FDR, first-degree relative; MAP, MUTYH-associated polyposis; MRI, magnetic resonance imaging; PJ, Peutz–Jeghers; PPAP, polymerase proofreading-associated polyposis; SP, serrated polyposis; TV, transvaginal; US, ultrasound.

Table 5. Spigelman classification for duodenal polyposis in familial adenomatous polyposis [47]

Variable	1 point	2 points	3 points
Number of polyps	1–4	5–20	>20
Polyp size (mm)	1–4	5–10	>10
Histology	Tubular	Tubulovillous	Villous
Dysplasia	Mild	Moderate	Severe

Stage 0, 0 points; stage I, 4 points; stage II, 5–6 points; stage III, 7–8 points; stage IV, 9–12 points.
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and/or antioestrogens), ChT, surgical excision or radiotherapy [48].

MUTYH-associated polyposis

Prevalence and penetrance. MAP is an autosomal recessive syndrome caused by biallelic germline mutations in the *MUTYH* gene and usually characterised by a phenotype of attenuated adenomatous polyposis and a lower risk of extracolonic manifestations in comparison with FAP.

The development of polyps in individuals carrying biallelic mutations in the *MUTYH* gene usually begins in the second or third decade of life. A CRC risk of 19% at 50 years and 43% at 60 years (with a mean age of 48 years) has been described [49]. The risk of duodenal adenomas is low.

Clinical and molecular diagnosis. The clinical spectrum of *MUTYH* germline mutations is heterogeneous, including attenuated and classic adenomatous polyposis, CRC without polyposis and Lynch-like syndrome. Biallelic *MUTYH* mutations should be suspected in patients with an attenuated form of adenomatous polyposis or classical FAP with a recessive pattern of inheritance. It should also be considered in CRC patients diagnosed before the age of 50 years, and in patients with multiple colonic polyps (>10, including both adenomatous and serrated ones).

The most prevalent mutations in the Caucasian population are *Y179C* and *G396D* [40]; however, there exist ethnic and geographical differences in the mutation landscape of this gene. The prevalence of *MUTYH* heterozygotes in the general population is 1%–2% [50].

Germline genetic testing should include all exons of *MUTYH*. With the incorporation of multigene panels, due to the substantial overlap of the clinical phenotype of polyposis syndromes, we recommend a multigene single analysis of the genes involved in colorectal adenomatous polyposis (*APC, MUTYH, POLE, POLD1, NTHL1*) [V, B].

Surveillance and risk reduction.
Colorectal surveillance: In patients with MAP, a first colonoscopy is recommended at the age of 18–20 years, and every 1–2 years (Table 4). When the polyps cannot be controlled endoscopically, colectomy with IRA should be considered in absence of rectal involvement; however, if rectal involvement is substantial, a total proctocolectomy with IPAA is indicated. After surgery is carried out, it is recommended to continue with 1–2-year surveillance intervals of the remaining colorectal segment [III, C] [44].

CRC screening in monoallelic mutation carriers is recommended as for FDRs of a patient with sporadic CRC. There is no evidence of the usefulness of chemoprevention in this condition.

Gastric and small bowel surveillance: In most cases, the surveillance strategy with upper endoscopy is determined based on the monitoring of duodenal polyps, carrying out a first endoscopy at 25–30 years and continuing depending on the Spigelman stage (Table 5) [47].

Polymerase proofreading-associated polyposis

Recent studies have identified two genes with autosomal dominant inheritance associated with multiple adenomas and early-onset CRC: *POLE* and *POLD1* [51]. Mutations in these genes have been related to different phenotypes that range from a classic phenotype with gastroduodenal involvement to attenuated forms or characteristic tumours of LS [52]. An approach similar to MAP is recommended with regular colonoscopy surveillance (Table 4).

Adenomatous polyposis associated with germinal mutation in *NTHL1*

Recent studies of whole exome sequencing have identified the association of biallelic germinal mutation of *NTHL1* (16p13.3) with attenuated adenomatous polyposis. This new polyposis syndrome has an autosomal recessive inheritance and probably an increased risk of EC in biallelic mutation carriers [53]. There are no specific recommendations for the management of these patients and an approach similar to MAP is recommended with regular colonoscopy surveillance.

Serrated polyposis syndrome

Prevalence and penetrance. Serrated polyposis syndrome (SPS) is a condition characterised by the combination of large and/or numerous serrated lesions spreading throughout the colorectum with an increased lifetime risk of CRC (15%–30%). While prevalence of SPS remains unknown, this syndrome is emerging as one of the most common CRC polyp syndromes [54, 55].

Clinical and molecular diagnosis. According to the World Health Organization (WHO) criteria developed in 2019 [56], SPS is defined as:

> Criterion 1: ≥5 serrated lesions/polyps proximal to the rectum, all being ≥5 mm in size, with ≥2 being ≥10 mm in size;
>
> Criterion 2: >20 serrated lesions/polyps of any size distributed throughout the large bowel, with ≥5 being proximal to the rectum.

Any histological subtype of serrated lesion/polyp (hyperplastic polyp, sessile serrated lesion without or with dysplasia, traditional serrated adenoma and unclassified serrated adenoma) is included in the final polyp count. The polyp count is cumulative over multiple colonoscopies.

The genetic basis of SPS remains largely unknown. Biallelic *MUTYH* mutations have been reported in some patients fulfilling the WHO criteria, usually in the context of a concomitant attenuated form of adenomatous polyposis. Recently, *RNF-43* germline mutations have been reported in some families with SPS [57].

Surveillance and risk reduction. Recent evidence suggests that surveillance with colonoscopy should be carried out every 1–2 years (it can be extended to 2 years in most patients based on certain risk factors, i.e. polyp multiplicity or advanced features) (Table 4) [III, C] [58, 59]. Although more evidence is needed, screening by colonoscopy every 5 years in FDRs of patients with SPS is commonly recommended, starting at the age of 45 years (or 10 years earlier than the age of diagnosis of the youngest affected family member) [60, 61]. There is no evidence to support extracolonic cancer surveillance in SPS patients [62].

Surgery is reserved to patients with CRC or those who cannot safely be managed endoscopically. Total colectomy with IRA is the technique of choice in patients with severe and recurrent polyposis, whereas segmental colectomy may be indicated in less severe cases. After colectomy, it is recommended to continue with 1–2-year surveillance intervals of the remaining colorectal segment [III, C].

Hamartomatous polyposis

Hamartomatous polyposis syndromes, such as Peutz–Jeghers syndrome (PJS) and juvenile polyposis syndrome are rare entities with diagnostic criteria and surveillance recommendations based on expert consensus (Table 4) [63] [IV, C].

Hereditary gastric cancer

The majority of GCs are sporadic. Familial clustering is observed in about 10% of the cases and 1%–3% are hereditary, encompassing hereditary diffuse GC (HDGC) and familial intestinal GC (FIGC). The stomach is also affected by gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) syndrome that was recently recognised as a rare variant of FAP. Furthermore, GC can develop in the setting of other hereditary cancer syndromes such as Li–Fraumeni syndrome (LFS), FAP, PJS, LS, hereditary breast/ovarian cancer syndrome (HBOCS), MAP and juvenile polyposis. The lifetime risk of GC in these syndromes varies substantially between populations studied but is generally low. A diagnostic algorithm for hereditary GC is shown in Figure 2.

Hereditary diffuse gastric cancer

Prevalence and penetrance. HDGC is an autosomal dominant cancer susceptibility syndrome characterised by signet ring cell (SRC) cancer/diffuse gastric cancer (DGC) and lobular breast cancer (LBC). *CDH1* gene, encoding for E-cadherin, was identified as a genetic cause of HDGC and recently the *CTNNA1* gene, encoding α–E-catenin, has also been implicated [64, 65]. The incidence of heterozygous *CTNNA1* germline mutation is low in families with DGC (~1%–2%).

HDGC accounts for <3% of the global burden of GC. The cumulative risk of DGC for *CDH1* mutation carriers by the age of 80 years is reported to be 70% for men and 56% for women [66]. The cumulative risk of LBC for women with a *CDH1* mutation is estimated to be 42% by 80 years. The age of onset of HDGC may be extremely variable (14–85 years).

Clinical and molecular diagnosis. Genetic testing for *CDH1* is recommended in families with clinical criteria of HDGC [III, A], Testing of germline *CDH1* alterations is recommended in

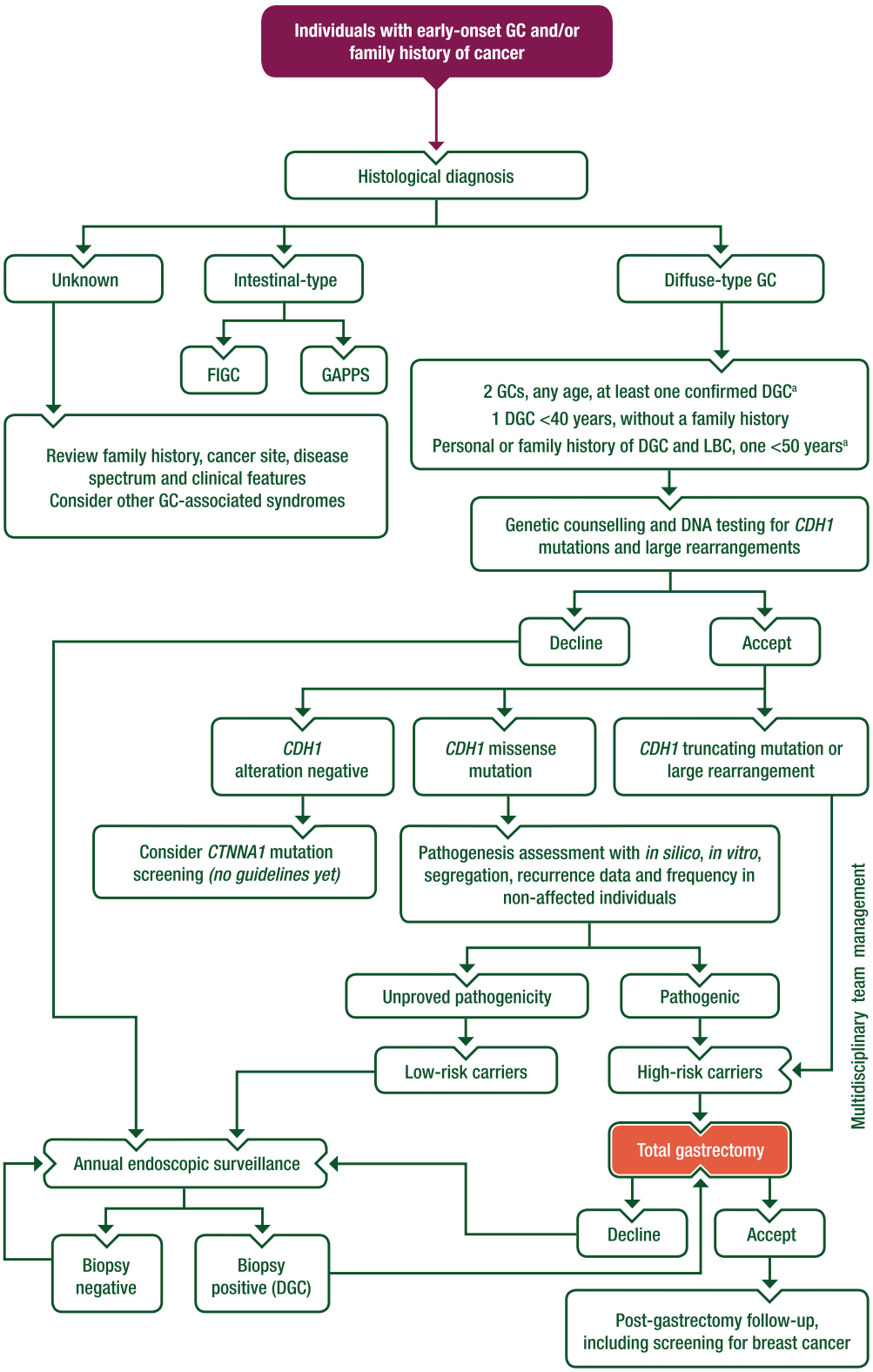

Figure 2. Algorithm for hereditary gastric cancer diagnosis.
[a]Including first- or second-degree relatives.
DGC, diffuse gastric cancer; FIGC, familial intestinal gastric cancer; GAPPS, gastric adenocarcinoma and proximal polyposis of the stomach; GC, gastric cancer; LBC, lobular breast cancer.

families that fulfil one of the following three criteria, according to the International Gastric Cancer Linkage Consortium (IGCLC) guidelines [66]:

- Two or more documented cases of GC at any age in first- or second-degree relatives, with at least one confirmed DGC;
- Personal history of DGC before the age of 40 years or
- Personal or family history (first- or second-degree relatives) of DGC and LBC, one diagnosed before the age of 50 years.

Genetic testing can be considered in families with bilateral or multiple cases of LBC before the age of 50 years, families with clustering of DGC and cleft lip/cleft palate and any patient diagnosed with *in situ* or pagetoid spread of SRCs [66].

The age at which at-risk relatives should be genetically tested should take into consideration the earliest age of cancer onset in that family. Testing from the late teens or early 20s is favoured in families with early-onset DGC [66].

Germline genetic testing should include both DNA sequencing and large rearrangement analysis. The identification of germline *CDH1* missense variants requires additional studies to assess their putative pathogenicity.

Surveillance and risk reduction.

Endoscopic surveillance and prophylactic surgery: Asymptomatic carriers of *CDH1* pathogenic germline mutations are offered prophylactic gastrectomy or, for selected groups, annual endoscopic surveillance [IV, B]. Surveillance with annual endoscopy is recommended for individuals aged <20 years, for those who decline prophylactic gastrectomy unless they have a positive biopsy, for those with comorbidities and for those with familial DGC and a variant of uncertain significance in *CDH1*. A minimum of 30 random biopsies in the endoscopy is recommended, as described in the Cambridge protocol [IV, B] [66]. Any malignant lesion detected endoscopically would prompt a referral for gastrectomy; however, all patients undergoing endoscopy for HDGC should be informed that given the very focal and often endoscopically invisible nature of these lesions, it is quite possible that lesions will not be detected by random biopsies.

Total gastrectomy is recommended between 20 and 30 years of age [IV, A]. In biopsy-positive individuals, a curative total gastrectomy is advised, regardless of age. Prophylactic gastrectomy at an age of >75 years should be carefully considered.

Breast cancer surveillance: Annual breast MRI with mammography starting at age 30 is recommended in women with a *CDH1* mutation [IV, B]. Annual clinical breast examination and breast cancer awareness by the patient and her physicians are essential.

Familial intestinal gastric cancer

Prevalence and penetrance. The diagnosis is considered when there is a family history of intestinal-type GC with an autosomal dominant inheritance pattern.

Clinical and molecular diagnosis. In 1999, the IGCLC proposed diagnostic criteria analogous to the Amsterdam criteria in high-incidence countries (e.g. Portugal, Japan).

Criteria in low-incidence countries include:

- At least two first- or second-degree relatives affected by intestinal GC, one of them diagnosed before the age of 50 years, or
- Three or more relatives with intestinal GC at any age [67].

The diagnosis is considered when there is a family history of intestinal-type GC in families without polyposis. The genetic cause of FIGC is currently unknown.

Surveillance and risk reduction. There is a lack of evidence to make robust recommendations for the management of individuals at risk of FIGC [68] [V, C]. Eradication of *H. pylori* is advised in family members of patients with intestinal GC at <40 years or in families with clustering of FIGC.

Gastric adenocarcinoma and proximal polyposis of the stomach

Prevalence and penetrance. GAPPS is an autosomal dominant cancer predisposition syndrome with a substantial risk of gastric, but not colorectal, adenocarcinoma [69].

Clinical and molecular diagnosis. Clinical criteria are required for the diagnosis of GAPPS:

- Gastric polyps restricted to the body and fundus with no evidence of colorectal or duodenal polyposis;
- >100 polyps carpeting the proximal stomach in the index case, or >30 polyps in an FDR of another case;
- Mainly fundic gastric polyps, some with regions of dysplasia (or a family member with either dysplastic fundic gastric polyps or gastric adenocarcinoma);
- Autosomal dominant pattern of inheritance;
- Exclusions include other hereditary gastric polyposis syndromes and use of proton-pump inhibitors [69].

GAPPS presents with incomplete penetrance. The age of onset of GC is variable (23–75 years; median 50 years) and the typical carpeting fundic gland polyposis with dysplasia has been detected as early as 10 years of age.

The genetic defect was identified as point mutations in the promoter 1B of the *APC* gene that co-segregated with disease in six GAPPS families [70]. Therefore, GAPPS is considered as an FAP variant with a predominant gastric phenotype.

Surveillance and risk reduction. The management includes endoscopic surveillance with random biopsies or preferably polypectomies directed to large/irregular polyps and, eventually, prophylactic gastrectomy. The limitations of endoscopic surveillance, the patient-specific risk of morbidity associated with prophylactic surgery and the risk of GC within the specific family need to be balanced [70, 71]. Due to the limited data available, individualised management is advised.

Hereditary pancreatic cancer

Prevalence and penetrance

Approximately 10% of patients with PC present a family cancer history. There are several hereditary syndromes associated with

Table 6. Summary of recommendations

Hereditary non-polyposis colorectal cancer syndrome (Lynch syndrome)

- Tumour testing with IHC for MMR proteins and/or MSI is recommended in individuals with CRC [III, A]
- If loss of *MLH1* is observed in the tumour, analysis of *BRAF V600E* mutation or analysis of the methylation of the *MLH1* promoter should be carried out first to rule out a sporadic case [III, B]
- Somatic *MMR* gene testing for patients with unexplained abnormal tumour screening is suggested [III, B]
- Clinical risk can be assessed using Amsterdam criteria II or the revised Bethesda guidelines
- MMR IHC and/or MSI screening, with *MLH1* promotor hypermethylation analysis in cases of MLH1 expression loss, is recommended for women with endometrial cancer [III, B]
- Full germline genetic testing should include DNA sequencing and large rearrangement analysis [III, A]
- Follow-up recommendations in mutation carriers include colonoscopy every 1–2 years [III, A], and gynaecological examination (with TV US, CA 125 and endometrial biopsy) on a yearly basis from age 30 to 35 years [IV, C]. In all cases, age of onset in the youngest member of the family is to be considered and surveillance be started 5 years earlier [V, B]. High-quality colonoscopy carried out in dedicated centres is advised [IV, C]. UGI endoscopy surveillance (every 1–3 years, from age 30–35 years) may be considered in patients at high risk. Prophylactic gynaecological surgery might be an option for female carriers who have completed childbearing or are postmenopausal [IV, C]

Cancer treatment

- Extended colectomy may be an option in patients undergoing primary surgery for CRC [IV, C]
- MMR or MSI status can be used to direct adjuvant ChT [II, C]
- Advanced MMR-deficient tumours may benefit from pembrolizumab or nivolumab

Other syndromes

- In familial CRC cancer X syndrome, colonoscopy surveillance (every 3–5 years) should generally start at age 40 years [IV, C]
- In Lynch-like syndrome, *MMR* genetic testing rules out sporadic somatic biallelic mutations

Hereditary polyposis colorectal cancer syndromes

- Patients with multiple colorectal adenomas (>10) should be considered for panel germline genetic testing that includes *APC, MUTYH, POLE, POLD1 and NTHL1* genes. *APC* analysis should include large rearrangements [III, A]
- In families with classic FAP, sigmoidoscopy should begin at the age of 12–15 years and be carried out every 1–2 years. Once adenomas are detected, colonoscopy should be carried out every 1–2 years until colectomy is planned. Surgery is indicated if there are large numbers of adenomas, or with a high degree of dysplasia [III, C]
- In families with AFAP, colonoscopy should be carried out every 2 years starting at the age of 18–20 years and continued lifelong in mutation carriers. Surgery is indicated if there are large numbers of adenomas. Some patients with AFAP can be conservatively managed with annual colonoscopy and polypectomy [III, C]
- The type of colorectal surgery in FAP (total colectomy + IRA versus proctocolectomy + IPAA) depends on the age of the patient, the severity of rectal polyposis and the risk of developing desmoid tumours [III, B]
- After colorectal surgery, surveillance of the rectum or pouch should be carried out [III, B]
- In both classic FAP and AFAP, screening for extracolonic manifestations (gastroduodenal polyposis, thyroid cancer, desmoid tumours) should start when colorectal polyposis is diagnosed or at the age of 25–30 years, whichever comes first [III, C]
- If adenomas are detected, surveillance should be guided by the Spigelman classification [III, B]
- Duodenal adenomas are usually managed by endoscopic polypectomy, although surgery (duodenectomy or duodenal-pancreatectomy) may be necessary in advanced cases
- Regular physical examination and abdominal CT or MRI should be conducted in patients who are at risk of developing desmoid tumours, with treatment options including NSAIDs and/or antioestrogens, ChT, surgical excision or RT

MAP

- Biallelic *MUTYH* mutations should be suspected in cases of AFAP or FAP with a recessive pattern of inheritance, diagnosis before the age of 50 years, and multiple colonic polyps
- A multigene single analysis of *APC, MUTYH* (all exons), *POLE, POLD1* and *NTHL1* is recommended [V, B]
- Colonoscopy should be conducted every 1–2 years from the age of 18–20 years
- Where endoscopic control is not possible, IRA or IPAA, depending on the degree of rectal involvement, followed by annual endoscopic surveillance, is recommended [III, C]
- CRC screening in monoallelic mutation carriers is recommended
- UGI endoscopic surveillance of duodenal polyps should begin at age 25–30 years and continue according to the Spigelman stage

Other syndromes

- For *POLE*- and *POLD1*-mutation-positive *PPAP* and *NTHL1*-mutation-positive adenomatous polyposis, colonoscopic surveillance should follow MAP recommendations
- In SPS, colonoscopic surveillance should be carried out every 1-2 years (it can be extended to 2 years in most patients, based on risk factors)
- In FDRs of patients with SPS, colonoscopic screening every 5 years, from age 45 years, is generally recommended
- In SPS patients with CRC or where disease cannot be managed endoscopically, total colectomy with IRA or segmental colectomy are indicated, followed by annual surveillance [III, C]

Continued

HDGC

- Genetic testing for *CDH1* is recommended in families with clinical criteria of hereditary diffuse gastric cancer [III, A]
- Testing of germline *CDH1* alterations is recommended in families fulfilling at least one of the IGCLC guidelines criteria
- Testing from late teens or early 20s is favoured in families with early-onset DGC
- Germline testing should include both DNA sequencing and large rearrangement analysis
- Annual endoscopy surveillance is recommended for individuals aged < 20 years, those declining gastrectomy and those with familial DGC and a *CDH1* variant of uncertain significance
- A minimum of 30 random biopsies is recommended [IV, B] and a curative gastrectomy is recommended for biopsy-positive individuals, regardless of age
- Total gastrectomy is recommended between 20 and 30 years of age [IV, A]
- Prophylactic gastrectomy is recommended in carriers of a pathogenic germline *CDH1* mutation between 20 and 30 years [IV, A], and annual breast MRI in female mutation carriers starting at age 30 [IV, B]
- Annual clinical breast examination and breast cancer awareness by the patient and her physicians are essential

Familial intestinal gastric cancer

- The diagnosis of FIGC is considered when there is a family history of intestinal-type GC in families without polyposis
- No robust recommendations can be made for the management of individuals at risk [V, C], but *Helicobacter pylori* eradication is advised in family members of patients with intestinal GC at < 40 years or in families with clustering of FIGC

Gastric adenocarcinoma and proximal polyposis of the stomach

- GAPPS is diagnosed according to the degree and distribution of gastric polyps and familial history
- Management should be individualised and includes endoscopic surveillance, with random biopsies or polypectomies, and eventual prophylactic gastrectomy

Hereditary PC

- Multigene panel testing, covering *BRCA1, BRCA2, PALB2, CDKN2A*, is recommended for families with a strong clustering of pancreatic cancer [IV, B]
- Surveillance generally begins at age 50 years (or 10 years earlier than the age of the youngest affected relative) [IV, B], and annual endoscopic ultrasonography and/or pancreatic MRI are the procedures of choice.
- Patients with HP or PJS are recommended to start surveillance at age 30 and 40, respectively
- For suspicious lesions, surgical intervention must be individualised
- Prophylactic pancreatectomy is not indicated in gene mutation carriers without any precursor lesion [V, A]

AFAP, attenuated familial adenomatous polyposis; APC, adenomatous polyposis coli; CA 125, cancer antigen 125; ChT, chemotherapy; CRC, colorectal cancer; CT, computed tomography; DGC, diffuse gastric cancer; FAP, familial adenomatous polyposis; FDR, first-degree relative; FIGC, familial intestinal gastric cancer; GAPPS, gastric adenocarcinoma and proximal polyposis of the stomach; GC, gastric cancer; HDGC, hereditary diffuse gastric cancer; HP, hereditary pancreatitis; IGCLC, International Gastric Cancer Linkage Consortium; IHC, immunohistochemistry; IPAA, ileal pouch-anal anastomosis; IRA, ileorectal anastomosis; MAP, MUTYH-associated polyposis; MMR, mismatch repair; MRI, magnetic resonance imaging; MSI, microsatellite instability; NSAID, non-steroidal anti-inflammatory drug; PC, pancreatic cancer PJS, Peutz-Jeghers syndrome; RT, radiotherapy; SPS, serrated polyposis syndrome; TV, transvaginal; UGI, upper gastrointestinal; US, ultrasound.

an increased risk of PC: HBOCS, familial atypical multiple mole melanoma (FAMMM), LS, FAP, ataxia telangiectasia (ATM), PJS and hereditary pancreatitis (HP). Of these syndromes, PJS and HP are associated with the highest accumulated risk for PC (36% and 18%–53%, respectively) [72, 73].

Clinical and molecular diagnosis

Diagnosis is usually based upon clinical criteria of the different syndromes associated, followed by a confirmation with a genetic test. These hereditary cancer syndromes account for approximately 10%–15% of hereditary PC cases, and the most common cause of hereditary PC is a mutation in the *BRCA2* gene [74].

In most families, the cause of hereditary PC is not identified. This is known as familial PC (FPC) and applies to families with two or more FDRs with PC who do not fulfil the criteria of any other inherited tumour syndrome. FPC accounts for ≤80% of clusters of families with PC. Some recent studies have reported germline mutations in the most frequent genes (*BRCA1*, *BRCA2*, *PALB2*, *CDKN2A*) related to hereditary pancreatic syndromes, even without other extrapancreatic manifestations. This suggests that a multigene panel approach in families with a strong clustering of PC is adequate [IV, B] [74].

Surveillance of high-risk patients

There is no solid evidence that screening is associated with a decrease in morbidity and mortality related to PC [28, 62, 75]. Based upon the International Cancer of the Pancreas Screening (CAPS) Consortium consensus, surveillance for PC is recommended in the following high-risk patients [28]:

- Individuals with three or more blood relatives affected with PC, with at least one affected FDR;
- Individuals with at least two affected FDRs with PC;
- Patients with PJS, regardless of family history of PC;
- *CDKN2A/p16* carriers with one affected FDR;
- *BRCA2* mutation carriers with one affected FDR (or two affected family members, no FDR) with PC;
- *PALB2* mutation carriers with one affected FDR; and
- *MMR* gene mutation carriers (LS) with one affected FDR.

Currently, annually endoscopic ultrasonography and/or pancreatic MRI are the procedures of choice for surveillance [62].

Table 7. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America—United States Public Health Service Grading System[a])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, expert opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America [76].

Surveillance programmes usually begin at age 50 (or 10 years earlier than the age of the youngest affected relative) [IV, B]. Patients with HP or PJS are recommended to start surveillance at age 30 and 40, respectively.

Surgical management in patients at high-risk for pancreatic cancer

If a suspicious lesion is detected, no consensus has been reached with respect to the extension of pancreatic resection (partial or total pancreatectomy). In this setting, a multidisciplinary team is needed and surgical intervention must be individualised. In gene mutation carriers without any precursor lesion, prophylactic pancreatectomy is not indicated [V, A].

Methodology

These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors. A summary of recommendations is shown in Table 6. Levels of evidence and grades of recommendation have been applied using the system shown in Table 7. Statements without grading were considered justified standard clinical practice by the experts and the ESMO Faculty. This manuscript has been subjected to an anonymous peer review process.

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